Fourteenth Annual Pezcoller Symposium: The Novel Dichotomy of Immune Interactions with Tumors

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ABSTRACT

The main focus of the Symposium was the fact that cell types of the innate and adaptive immune systems can have tumor-favoring as well as tumor antagonistic effects, both in a preventive and therapeutic mode. It was shown that macrophages (MΦ) and dendritic cells within a tumor exert tumor-favoring effects through the action of certain cytokines. Inflammatory reactions could favor the onset and growth of tumors. Dual immune functions were shown with CD4+ T cells and certain matrix metalloproteinase (MMP) activities favoring tumor progression and CD8+ T cells and certain heat shock proteins having antitumor action. Lack of antitumor action despite positive immune stimulation was also shown to depend on the existence of barriers to tumor infiltration by lymphocytes; remodeling of vasculature, e.g., by IFN-γ-induced cytokines like MIG and IP10, reversed this type of impediment. Certain CXC cytokines increased tumor progression, whereas others, particularly those induced by IFN-γ, had the opposite effect; stromal-derived factor-1 and its receptor CXCR4 affected tumor propensity to metastasize in certain organs. Stromal-derived factor-1 induced MMP9, which in turn regulated the bioavailability of vascular endothelial growth factor and the cascade of its tumor-favoring effects, whereas granulocyte colony-stimulating factor decreased MMP9 and the consequences of its action. The effects of certain proinflammatory cytokines and vascular endothelial growth factor functions in angiogenesis and lymphoangiogenesis were also discussed. The favoring effects of fever-like thermal stress on the function of molecules instrumental in lymphoid cell adhesion to vessels and infiltration into sites of immune actions were described. The mechanisms involved in the development of immune memory and those conditioning Type I and CTL responses were also discussed. A number of presentations were concerned with laboratory studies aimed at developing clinical regimens with potential activity in the prevention or treatment of cancer. Prevention of Her2/neu breast cancer in transgenic mice was achieved by suitable regimens with IL12 combined with vaccines, including DNA-based vaccines administered in conjunction with electroporation. Vaccination with shared tumor antigen MUC1 or cyclin B was discussed, and its clinical translation was described. The prevention of TRAMP prostate tumor in transgenic mice by anti-CTLA4 antibody plus vaccine was described, as translation was described. The prevention of TRAMP prostate tumor in transgenic mice by anti-CTLA4 antibody plus vaccine was described, as was the translation of these regimens to the clinics. Clinical successes in melanoma patients using antimelanoma antigen antibodies in a therapeutic mode and precautions to be exerted in evaluating in vivo immune responses based on in vitro assays were emphasized. The symposium was concluded with an overall discussion focused on basic questions related to the capability of immunity to exert tumor-favoring or antitumor effects depending on conditions determined by both tumor and host functions.

I. Antitumor and Tumor Favoring Effects and Effectors

It is becoming increasingly evident that host responses to tumor, whether strictly immunological or inflammatory in nature, may have dual and opposite effects on tumor progression. These opposite effects were a main focus of discussion.

Inflammation and Innate Immunity: Effects on Tumor Progression.

Alberto Mantovani discussed the function of macrophages (MΦ) and DCs which are present in neoplastic tissues. The recruitment and distribution in tumors of these cells are guided by specific cytokines. The CC chemokine CCL18-PARC is produced by MΦ in tumors and has been found, e.g., in the ascites of ovarian cancer. The tumor-derived chemotactic factor MCP-1 is also affecting MΦ infiltration in tumors with consequent tumor-favoring effects. Tumor or lipopolysaccharide induce in MΦ genes encoding inflammatory cytokines and their receptors, e.g., IL1β, certain MMPs, and CC-chemokines ligand. The ensuing inflammatory processes and extracellular matrix digestion favor tumor cell progression, migration, and metastasis. Cytokines activate a specific transcriptional program in human monocytes. Functional and genetic evaluation showed that tumor-infiltrating MΦ have a skewed type 2 phenotype. The first long pentraxin PTX3 was cloned by this group and is a new soluble innate immunity receptor whose COOH terminus is analogous to that of C-reactive protein, with unrelated NH2 terminus. In some systems, this molecule plays a role in innate immunity and inflammation and causes antitumor effects. As a whole, the data available emphasize the dual effects of inflammatory molecules ranging from tumor promotion to antitumor action depending on conditions.

Masuo Hosokawa demonstrated that progression of a weakly tumorigenic C57BL/6 mouse fibrosarcoma (QR-32) is favored by inflammatory processes. The QR-32 cells grow progressively only when coimplanted with a gelatin sponge. The growth of QR-32 cells implanted with the foreign body was associated with inflammation and the presence of a variety of cell types; thus, natural killer cells, lymphokine-activated killer cells, MΦ, and PMN could promote tumor growth, but T cells could not. Depletion of PMN by the injection of glutamic acid, leucine and arginine residues antitumor PMN antibody prevented the tumor growth-favoring effects of the gelatin implant and related inflammation as did the administration of an anti-inflammatory nonsteroidal agent. Tumor progression was also inhibited by Polysaccharide K or Lentinan, which increased the amount of antioxidant enzymes and decreased the production of reactive oxygen radicals.

Dylan Daniel provided evidence that in a transgenic mouse with multistage squamous cell carcinoma induced by HPV oncogenes, activated infiltrating CD4 T cells enhance tumor development and progression. In fact, in CD4T-deficient mice, there was a ~2-month delay in the onset of tumors, and the incidence of premalignant dysplasia was reduced; no such effect was seen in crosses with CD8 T cell-deficient mice. The delay in carcinogenesis seen in the CD4 T-deficient crosses was accompanied by a decreased infiltration of neutrophils and a decreased activity of matrix MMP-9/gelatinaseB; MMP9 can mobilize growth factors, causing a degradation of ECM, and has a role in favoring tumor growth. In MMP-9 knockout HPV mice, the onset of tumor was much delayed. In contrast to the tumor-favoring effects of CD4 T cells during skin carcinogenesis, treatments of HPV female mice developing cervical cancer with HSV 65/HPV16-E7 fusion protein-primed CD4 T cells caused responses to HPV16 and had antitumor effects. Thus, examples were provided indicating that proinflammatory CD4+ T cells had tumor-favoring effects in one organ, whereas in another organ, CD4 T cells could be primed to exert antitumor effects.

The abbreviations used are: DC, dendritic cell; MMP, matrix metalloproteinase; PMN, polymorphonuclear; HPV, human papillomavirus; HSV, heat shock protein; VEGF, vascular endothelial growth factor; NSCLC, non-small cell lung cancer; SCID, severe combined immunodeficiency; ERK, extracellular signal-regulated kinase; ELR, glutamic acid, leucine and arginine residues; SDF, stromal-derived factor; APC, adenomatous polyposis coli; GM-CSF, granulocyte colony-stimulating factor.

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1 This symposium was held May 30 to June 1, 2002 in Trento, Italy. The symposium was cochaired by Drs. Douglas Hanahan (University of California at San Francisco, San Francisco, California), Antonio Lanzavecchia (Institute of Research in Biomedicine, Bellinzona, Switzerland), and Enrico Mihich (Roswell Park Cancer Institute, Buffalo, New York).
**Tumor Angiogenesis: Relationships to Immunity and Inflammation.**

Ruth Ganss discussed the role of tumor endothelium as a barrier to immune T-cell infiltration. Despite the presence of tumor antigen in regional lymph nodes and consequent activation of T cells, these cells are in an autophagosome model unable to migrate into tumor and exert their antitumor function. Indeed, at the interface between blood and tissues, well-integrated actions of cytokines and adhesion molecules, as well as intracellular signaling sequences, condition leukocyte extravasation; tumor angiogenesis may lead to the formation of vessels incompatible with this extravasation. Indeed, in the RIP1-Tag5 transgenic mouse model, β cell pancreatic tumors do not have infiltrating lymphocytes despite the presence of T antigen and activated T cells in the draining lymph nodes. It was found that leukocyte endothelium interactions were greatly reduced throughout tumorogenesis. Adoptive transfer of activated antitumor T cells was ineffective as was X-irradiation alone, whereas the combination of these two treatments led to tumor capillary network with almost normal appearance and a complete tumor regression. The infiltrating cells expressed IL12, which stimulated IFNγ, which in turn induced MIG and IP10. These two chemokines may contribute to the remodeling of the tumor vasculature toward normalization.

Zena Werb, after briefly reviewing current knowledge about MMPs as mediators of inflammatory cell functions in cancer, discussed results of her laboratory, indicating that gelatinase B/MMP9 made by inflammatory cells regulates angiogenesis and tumor growth through regulation of the bioavailability of VEGF. In turn, VEGF activates endothelial cells and thus prompts angiogenesis and tumor regression. It was also shown that MMP could promote or inhibit tumor growth depending on conditions.

In studies using the RipTag2 pancreatic islet tumor model, it was found that MMP9 appears at the time of the angiogenic switch and releases VEGF, thus rendering normal islets angiogenic. Indeed, in MMP9 knockout mice, the formation of the VEGF-receptor complex is delayed, and angiogenic switch, tumor numbers, and growth are reduced. MMP9 also regulates the recruitment of angiogenic cell progenitors by VEGF. In the bone marrow, the mRNA of MMP9 is increased, and these levels are decreased after treatment with 5-fluorouracil. MMP-9 was also capable of releasing c-kit ligand from the c-kit complex. In human CD34+ stem cells, SDF-1 induces increases of MMP9. It was also found that MMP9 is needed for the GM-CSF-dependent reconstitution of bone marrow. The VEGF-dependent mobilization of epithelial cell progenitors is decreased in MMP9 knockout mice. In summary, increases of SDF-1 and VEGF induce increases of MMP9, which lead to the release of soluble c-kit ligand, and this causes the recruitment of several progenitor c-kit+ cells and their formation of sinusoid vessels.

Kari Alitalo outlined the role of certain growth factors and gene programs in lymphangiogenesis. VEGF-A regulates angiogenesis and permeability of blood vessels through its binding to 2 receptors, VEGFR-1 and VEGFR-2; the role of VEGF-C, which is not mediated by VEGFR, is still not understood. Normal lymphangiogenesis is driven by VEGF-C and VEGF-D and is dependent on CXCR2 and CXCR4. The proadhesive activity of IL-6/soluble IL-6 receptor complexes is also increased in cancer patients undergoing fever range whole body hyperthermia therapy. These findings highlight a novel mechanism by which lymphocyte trafficking is amplified during physiological febrile responses and clinical thermal therapy.

**Regulation of Antitumor Immunity.**

Harvey Cantor discussed the regulation of Type 1 immunity with reference to its role in tumor rejection. The expression of early T-lymphocyte activation factor (Eta-1, Osteopontin), a phosphorylated protein secreted by certain activated T cells, has a critical role in Type 1 immunity and Th1 development. The expression of Eta-1 leads to up-regulation of IL12 and down-regulation of IL10, thus leading to increased Type 1 immunity and development of cytotoxic T cells. Using the transgenic mouse TRAMP prostate tumor model, it was shown that tumor progression in Eta-1 knockout mice was delayed in normal transgenic mice given Eta-based vaccination with or without anti-CTLA4 antibody; analogous results seemed to be obtained in melanoma.

Antonio Lanzavecchia provided evidence supporting the notion that memory cells are originated as a consequence of a weaker or shorter antigen stimulation than that leading to the development of differentiated effectors. Those cells do not reach their terminal differentiation stage and remain at an intermediate stage, without effector function, and home in lymph nodes. The clonally expanded intermediate cells mediate prompt recall responses and represent “central memory” cells. These memory cells behave like “memory stem cells” in the sense that they are capable of self-renewal in the absence of
antigen. DCs have a role in the function of both T effector cells and interme-
diate memory cells within the same clone.

A short T-cell receptor stimulation does not lead to the production of homeostatic lymphokines like IL7 and IL15, and the stimulated cells die. CD4 and CD8 cells have a similar dependence on the length of antigen stimulation; the CD4 and CD8 central memory T cells proliferate and differentiate in response to homeostatic cytokines and thus provide the mechanism for the production of T effector cells. It was emphasized that a multiplicity of reasons determine the development of effect T cells as contrasted with that of the central memory T cells.

II. Clinical Perspectives

Laboratory studies of the control mechanism of antitumor immunity were discussed in light of their potential translation to the clinics.

**Vaccination.** Guido Forni discussed the possibility that a measure of autoimmunity to p185<sup>neu</sup>-positive cells may provide effective prevention of the development of aggressive Her2<sup>neu</sup> mammary carcinomas. Consequent to p185<sup>neu</sup> overexpression in mouse mammary tumor virus-<i>neu</i> transgenic mice, atypical hyperplasia foci occur at 6 weeks of age and carcinoma in situ by 20 weeks, with tumors becoming palpable at 33 weeks. In one prevention strategy, repeated vaccination with DNA coding for the extracellular and transmem-
brane domains of rat-p185<sup>neu</sup> greatly retarded the onset of tumors. In a second strategy, vaccination with allogenic mammary carcinoma cells expressing both p185<sup>neu</sup> and H-29 class I molecules followed by prolong treatments with IL12 halted mammary carcinogenesis over a 1-year period. Treatment with IL12 increased nonspecific as well as specific immunity; it activated T cells; increased levels of IFN<sub>γ</sub>, TNFα, GM-CSF, IP<sub>10</sub>, INOS, MIG, and other cytokines; but it decreased levels of VEGF. Delayed-type hypersensitivity and increased antibody production were the main effects seen. These results indicated that preneoplastic changes can be a target for specific immunological effects. Treatment of mice bearing in situ carcinomas with DNA given by electroporation caused the majority of the mice to be tumor free. It was found that this effect was mediated by increased IFNγ-induced intratumor CD8<sup>+</sup> T-cell responses (delayed type hypersensitivity) and increased antibody; in IFNγ or immunoglobulin knockout mice, no such effects were seen. Adoptive transfer of T cells from mice treated with DNA via electroporation was very effective. The stage of carcinoma in situ during the process of carcinogenesis was the last point in time when these treatments could be effective.

Olivera Finn discussed the opportunities offered by the use of tumor antigens MUC1 and cyclin B1 as cancer vaccines. MUC1 mucin was discovered by this group as the first shared tumor antigen recognized by T cells. This mucin undergoes changes in glycosylation and three-dimensional structure on epithelial adenocarcinoma cells. These changes condition antigen presentation by APC, whereas soluble circulating MUC1 produced by tumor cells cannot be processed by the patient’s APC; therefore, a low frequency of T cells and low IgM titers are produced. In contrast, an unglycosylated form of MUC1 intro-
duced through vaccination is processed by DC and then MUC1-specific T helper cells. CTL and multiple IgG antibody isoatypes are produced; T cells are recruited to the antigen site and respond after the first vaccination, less so after the second one. It was shown in patients with breast, colon, and pancreatic cancer undergoing Phase I trials of MUC1 100-mer peptide that they are immunocompromised. Animal studies showed that the vaccine works best in a prevention mode. MUC1 was also found on premalignant cells, e.g., on adenomatous polyps in colon. Production of IFNγ, TNFα, or IL2 by patients’ T cells is decreased by oxygen peroxide. It was demonstrated that the ability to respond to vaccination was negatively affected by innate inflammatory responses.

Cyclin B1 was recently found to be a shared tumor antigen for tumor-
specific T-cell responses; it is a cell cycle regulator that is expressed at the G<sub>2</sub>-M interphase in large amounts in tumor but not in normal cells. In addition to the T-cell responses seen, e.g., in patients with pancreatic cancer, IgG and IgA isoatypes are also produced. Solid tumors of different types, as well as lymphomas, express cyclin B1 and all have functionally inactive P53; P53 inactivation and increased expression of cyclin B1 occur early during neoplastic transformation. A P53 knockout mouse provides a good model for the study of the expression of cyclin B1 and for its use as a vaccine in cancer prevention.

Giorgio Parmiani described the effects in metastatic melanoma patients of vaccination with autologous HSP 96 peptide complex (HSPPC-96). It is now apparent that HSPs activate APCs and increase innate immunity; HSPPC-96 includes chaperoned peptides whose uptake is receptor mediated and which elicits a polyclonal response. Melanoma-derived HSP70 increases recognition of gp100 and MART melanoma antigens. HSPP6 obtained from melanoma lines also increased tumor-specific T cells. HSPPC-96 was developed using HSP96 isolated from autologous melanoma patients and used to vaccinate stage 4 melanoma patients; among 28 individuals with measurable disease posturgery, 2 had complete responses, 8 had stable disease, and 18 had progressive disease. No difference in outcome could be discerned depending on route or dose of vaccine. Using an Elispot and HLAR tetramer staining assays, it was found that HSPPC-96 contained melanoma epitopes and was able to expand in vivo the anti-Melan-A/MART-1 T cells in 50% of vaccinated patients; reactivity to this antigen appeared to correlate with clinical response.

**Immunomodulation.** James Allison discussed new information on the mechanisms of negative costimulation by CTLA-4 and on the possibility of manipulating it in tumor immunotherapy. Recognition of MHC-antigen complexes by T-cell antigen receptors (T-cell receptor) also required positive and negative costimulatory signals for T-cell activation. Thus, interaction of CD28 on T cells with B7 family members on APC provides positive signals, whereas interaction of CTLA-4 on T cells with B7 on APCs provides negative signals; CTLA-4 has greater avidity than CD28 for B7, and it is induced and found in intracellular vesicles, whereas CD28 is constitutively expressed on the plasma membrane. A stimulatory signal specifically regulates the expression of CTLA-4, as well as its recruitment to functional relevant sites on the cell surface. The half-life of CTLA-4 is short; the molecule is located in the back of migrating cells, whereas CD28 is located all around the cell. In addition to inhibiting T-cell activation, CTLA-4 also restricts T-cell proliferation through inhibition of IL2 and cyclin-dependent kinase functions. Blocking CTLA-4 signals with anti-CTLA-4 antibodies allows much greater T-cell responses in mice, and these are sufficient to cause rejection of highly immunogenic tumors followed by memory. In the case of tumors with low immunogenicity, e.g., B16 melanoma, the administration of anti-CTLA-4 antibody plus irradiated GM-CSF-producing tumor cell vaccines causes propylactic immunity and tumor rejection, the latter accompanied by autoimmune depigmentation. The antitumor effects are mediated through the induction of a CD8<sup>+</sup> T-cell response against the melanocyte differentiation antigen TRP-2. In this setting, antitumor response is independent of CD4<sup>+</sup> T cells; in fact, the antitumor response was more effective in the absence of CD4<sup>+</sup> T cells, particularly CD25<sup>+</sup> CD4<sup>+</sup> Treg cells. In contrast, in a preventive mode, the administration of anti CD8<sup>+</sup> or anti-natural killer cell antibodies had no effect. Phase I trials of human anti-CTLA-4 antibodies have been completed in patients with prostate cancer and melanoma; the treatment was found to be safe, and there was evidence of antitumor activity in both trials.

Francesco Marincola discussed interactions between tumor and host with particular reference to malignant melanoma and methodologies to be best used to magnify the fidelity of measurements of immune effector activities as they are actually present in patients, e.g., in ex vivo analysis of the activation and differentiation of vaccination-induced T cells, it was found that circulating T cells respond to specific antigen with cytokine production (e.g., IFNγ) but have limited expression of effector molecules and display a “resisting” phenotype; this phenotype can be reversed on in vitro culturing in the presence of IL2. Indeed, the analysis of immune response in the peripheral circulation may not reflect the interactions occurring at the tumor site, where they are most relevant. Fine needle aspiration biopsies of metastatic melanoma provided samples on which the genetic profile could be studied by microarray technolo-
gies. Some tumors showed a genetic profile favoring immune responsiveness before treatment. Moreover, systemic IL2 induced or enhanced an inflamma-
tory state within the tumor. On the basis of the genetic profiles identified, it was assumed that IL2 induces IFNγ and other proinflammatory cytokines. This in situ inflammatory reaction is likely to be followed by activation of APC, production of chemotactants, and activation of lytic mechanisms of innate immunity. It was concluded that monitoring tumor/host interactions both in circulating immune cells and the tumor may provide for an understanding of the mechanisms of tumor regression in humans and may stimulate new ideas for the development of effective anticancer immunotherapy.

At the conclusion of the symposium, Douglas Hanahan moderated a round-
table discussion focused on basic questions related to the capability of immu-
nity to be pro and antitumor in its effects. Questions were asked about the protumor effects of inflammation-related processes; would it be possible to
inhibit the tumor-enhancing functions of infiltrating leukocytes? What are the functional relationships between innate immunity and inflammation in terms of pro or antitumor effects; might vaccines inadvertently increase tumor progression consequent to insufficient lesional destruction? What are the biological processes affecting solid tumors (e.g., interstitial pressure, chemokines, vascular adhesion, and others), which determine barriers to the onset of productive antitumor responses? Are the differences between pro and antitumor phenomena derived from qualitative or quantitative differences or both?

Poster presentations were included in the symposium, which are summarized on the Internet. 4

Noonan outlined the implications in cancer and AIDS of the angiostatin-dependent inhibition of phagocyte-mediated angiogenesis; Indraccolo evaluated comparatively the antitumor activity of angiogenesis inhibitors delivered by viral vectors. Entschladen outlined the bidirectional regulation of tumor cells and leukocyte migration by neurotransmittal and chemokines; Pacor indicated that the increase of lymphocyte activity after treatment with NAMI-A, a ruthenium-based compound, contributes to the eradication of solid tumor metastasis. Sartoris showed that the induction of antitumor immune memory with plasmacytoma-derived tumor cells expressing B7-1 is dependent on the immunization protocol; Turatti asked the question whether in redirected lysis by chimeric immune receptors specificity and affinity are in parallel, van der Voort asked whether the expression of DC-attracting chemokines by tumor cells induce antitumor immune responses; Bankert showed that human CD4+ T cells within human lung tumor microenvironment are mobilized by the local and sustained release of IL12 to kill tumors in situ. Carrabba indicated that tumor expression of Melan-A/Mart-1-altered peptide ligands contribute to suboptimal recognition by CD8+ T cells and that optimized analogues may generate T cells overcoming tumor-induced immunosuppression.

Appendix

The program committee consisted of the cochairs, Zena Werb (University of California, San Francisco, CA) and James Allison (University of California, Berkeley, CA). In addition to the program committee members, invited participants included: Adriana Albini (Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy), Kari Alitalo (University of Helsinki, Helsinki, Finland), Richard Bankert (University of New York at Buffalo, Buffalo, NY), Harvey Cantor (Dana-Farber Cancer Institute, Boston, MA), Mario Colombo (Istituto Nazionale Tumori, Milano, Italy), Dylan Daniel (University of California), Sharon Evans (Roswell Park Cancer Institute, Buffalo, NY), Soldano Ferrone (Roswell Park Cancer Institute, Buffalo, NY), Olja Finn (University of Pittsburgh, Pittsburgh, PA), Guido Forni (Ospedale S. Luigi Gonzaga, Orbassano, Italy), Ruth Ganss (German Cancer Research Center, Heidelberg, Germany), Siamon Gordon (University of Oxford, Oxford, United Kingdom), Masuo Hosokawa (Institute for Genetic Medicine, Sapporo, Japan), Eva Klein (Karolinska Institute, Stockholm, Sweden), Alberto Mantovani (Istituto Mario Negri, Milano, Italy), Francesco Marincola (National Cancer Institute, Bethesda, MD) Drew Pardoll (Johns Hopkins University, Baltimore, MD), Giorgio Parmiani (Istituto Nazionale Tumori), Hans Schreiber (University of Chicago, Chicago, IL), Robert Strieter (University of California, Los Angeles, CA), and Kurt Zanker (University of Witten, Witten, Germany).

The posters were presented by Douglas Noonan (Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy), Stefano Indraccolo (University of Padua, Padua, Italy), Frank Entschladen (University of Witten), Marina Bacac (University of Trieste, Trieste, Italy), Silvia Sartoris (University of Verona School of Medicine, Verona, Italy), Fabio Turatti (Istituto Nazionale Tumori), Robbert van der Voort (University Medical Center St. Radboud, Nijmegen, the Netherlands), Richard Bankert (University of New York at Buffalo), and Matteo Carrabba (Istituto Nazionale Tumori).

4 Supplementary data for this article are available at Cancer Research Online (Internet address: http://cancerres.aacrjournals.org).
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